UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/573,176 | 03/23/2006 | Wolfgang Staehle | MERCK3155 | 6633 |

23599 7590 02/20/2009

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

| EXAMINER | |
|---|---|
| FIERRO, ALICIA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 4121 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 02/20/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/573,176 | STAEHLE ET AL. | |
| | Examiner | Art Unit | |
| | ALICIA L. FIERRO | 4121 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11 and 14-38* is/are pending in the application.

4a) Of the above claim(s) *6 and 14-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7-11, 30-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *23 Mar 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Claims*

1. Claims 1-11 and 14-38 are pending in the instant application, filed March 23, 2005. Further, in the amended *Listing of the Claims*, claims 2-11 and 14-29 were amended, claims 30-38 were added, and claims 12-13 were cancelled.

### *Priority*

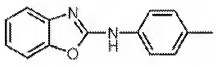
2. The instant application is a national stage entry of PCT/EP2004/09743, filed September 1, 2004, which claims priority to German Patent Application No. 103-44-223.5, filed September 24, 2003.

### *Information Disclosure Statement*

3. The information disclosure statement submitted on March 23, 2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed be submitted to the office. It has been placed in the application file, but the references which are crossed out in the signed copy of the 1449 form have not been considered.

### *Election/Restrictions*

4. Applicant's election with traverse of Group I, Claims 1-11 and 30-38 in the reply filed on January 16, 2009, as well as an election of the species (5-Chloro-7-nitrobenzoxazol-2-yl)-[4-(pyridine-4-ylsulfanyl)phenyl]amine) is acknowledged. The traversal is on the ground(s) that the present application does not lack unity because the special technical feature is a compound represented by formula (I), with the "common significant structural element" shown below:



Applicant's representative asserts that, in Markush practice, "alternatives will be regarded as fulfilling the criteria of being of a similar nature if the alternatives have a common property/activity and have a common significant structural element," and that because the instantly claimed compounds share a "common significant structural element," the unity of invention requirements have been met. This is not found persuasive for the following reasons.

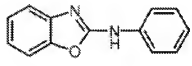
An international application should relate to only one invention or, if there is more than one invention, the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept (PCT Rule 13.1). With respect to a group of inventions claimed in an international application, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features.

The claims herein lack unity of invention under PCT rule 13.1 and 13.2 since, under 37 CFR 1.475(a):

Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions

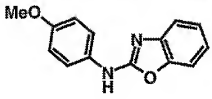
involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Groups I-IV lack unity of invention since under 37 CFR 1.475: the technical feature corresponding to the claims is shown below:



This is the core technical feature because it is the only **non-variable** core that is common to all compounds of formula (I). The presence of a common structural element is noted. However, the common structural element does not constitute a special technical feature because it fails to define a contribution over the prior art as can be seen in US 2003/0225131, which discloses the same core as in instant Claim 1. Applicant's representative asserts that because the prior art structure does not show a para-substituted phenyl ring, it does not show all common structural features. However, the para-substitution on compounds of formula (I) links to a portion of the compound that varies greatly in structure, and therefore does not constitute a portion of the **non-variable core** of the claimed compounds. It is noted, however, that even if the para-substitution is considered a part of the non-variable core structure, the "common significant structural element" still does not make a contribution over the prior art. See, for example, Example 10 in the specification of WO 02/076960, structure shown below:

**Example 10. N2-(4-Methoxyphenyl)-1,3-benzoxazol-2-amine**




Therefore, claims 1-11 and 14-29 are not so linked as to form a single general inventive concept and there is a lack of unity of invention because they lack a special technical feature as the technical feature present fails to define a contribution over the prior art. The core technical feature that is being claimed is taught by the prior art. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper.

Furthermore, in regards to Groups (I/II) and (III/IV), even if unity of invention under 37 CFR 1.475(a) is not considered lacking, which it is as evidenced above, unity is lacking under 37 CFR 1.475(b). Under 37 CFR 1.475(b): A national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn *only to one* of the following combinations:

(1) A product and a process specially adapted for the manufacture of said product; or

(2) A product and a process of use of said product; or

(3) A product, a process specially adapted for the manufacture of said product, and a use of said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of said product, and an

apparatus or means specifically designed for carrying out the said process.

And according to 37 CFR 1.475(c): if an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph 37 CFR 1.475(b), unity of invention might not be present.

Therefore, since the claims are drawn to compounds and compositions, which do not make a contribution over the prior art, as well as *various* methods of using the compounds of formula I, as in claims 14 through 29, and according to 37 CFR 1.475(e), the claims are deemed to lack unity of invention.

Therefore, since the claims do not relate to a single general inventive concept under PCT Rule 13.1 and lack the same or corresponding special technical feature, the claims lack unity of invention.

Applicants also traverse the restriction requirement on the grounds that "35 USC § 121 does not permit restriction within a single claim" (page 15 of Applicant's Response). This requirement states that if the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they may be directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require provisional election of a single species. See MPEP § 808.02. It is noted, however, that search and examination burden do not have to be demonstrated to establish lack of unity. Additionally, as Applicant's representative states on page 16 of the Response, since the decisions in In re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ

334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. As established in the Examiner's response above, it has been demonstrated that the claims do not meet the unity of invention requirement, and therefore the restriction requirement is deemed proper.

Finally, Applicants traverse that restriction requirement on the grounds that the requirement "presents no rationale as to why the methods of using the compounds recited in the claims of Groups III/IV are being restricted from the compounds of Groups I/II." Furthermore, the Response states that "an independent product claim, an independent process specially adapted to manufacture the product, and an independent claim for use of the product is a permissible combination." However, the rationale for the restriction between Groups I/II and III/IV lies in the lack of unity of invention according to PCT Rule 13.1, which is a result of the failure of the invariable core of the instantly claimed compounds to make a contribution over the prior art.

Under 37 CFR 1.475(b), a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn *only to one* of the following combinations:

(1) A product and a process specially adapted for the manufacture of said product; or

(2) A product and a process of use of said product; or

(3) A product, a process specially adapted for the manufacture of said product, and a use of said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said

process; or

(5) A product, a process specially adapted for the manufacture of said product, and an apparatus or means specifically designed for carrying out the said process.

And according to 37 CFR 1.475(c): if an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph 37 CFR 1.475(b), unity of invention might not be present.

Therefore, since the claims are drawn to compounds and compositions, which do not make a contribution over the prior art, a process specially adapted for the manufacture of said product, as well as *various* methods of using the compounds of formula I, as in claims 14 through 29, and according to 37 CFR 1.475(e), the claims are deemed to lack unity of invention.

Therefore, since the claims do not relate to a single general inventive concept under PCT Rule 13.1 and lack the same or corresponding special technical feature, the claims lack unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 6 and 14-29 are withdrawn as being drawn to non-elected subject matter. MPEP § 803.02 provides guidelines for election of species in Markush-type claims. These guidelines were followed for the search and examination detailed herein. In a search of the prior art, Applicant's elected compound (5-Chloro-7-nitrobenzoxazol-2-yl)-[4-(pyridine-4-ylsulfanyl)phenyl]amine was not found. Thus, the scope of the Markush claim has been extended to the next specie of a compound of formula I, or a pharmaceutically acceptable salt, derivative, solvate, or stereoisomer thereof. The species that was examined is carbon dioxide,

which is a derivative of compounds of formula (I). Because this species was not found to be free of the prior art, the search was not extended past this species.

5. Therefore, the Markush-type claims were rejected and the subject matter drawn to nonelected species held withdrawn from further consideration. Claims 1-11 and 30-38 were further examined, pursuant to MPEP § 803.02, to the extent necessary to determine patentability. It has been determined that the entire scope claimed is not patentable.

***Claim Objections***

6. Claims 1-5, 7-11, and 30-38 are objected to for containing non-elected subject matter.

7. Claim 7 is objected to. In proper Markush practice, the second to last and last members of the Markush groups should be separated by the word "and." Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

***(First Paragraph)***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-5, 7-11 and 30-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5, 7-11 and 30-38 recite the limitation, "derivatives…thereof" in reference to the instantly claimed compounds and their "derivatives." Applicant has not described the claimed genus of "derivatives" in a manner that would indicate they were in possession of the full scope of this genus, or even to describe what this genus is comprised of.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." Eli Lilly, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter aria*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although Eli Lilly and Enzo were decided within the factual context of DNA sequences, this does not preclude

extending the reasoning of those cases to chemical structures in general. Univ. of Rochester v. G.D. Searle & Co., 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, the claims are drawn to the compound (5-Chloro-7-nitrobenzoxazol-2-yl)-[4-(pyridine-4-ylsulfanyl)phenyl]amine or a composition of said compound, which falls within the general structure of formula (I), or a pharmaceutically acceptable salt, derivative, solvate, or stereoisomer thereof. The claimed "derivatives…thereof" encompass any compound that contains the identical core as the instantly claimed compound, with a differing of substituents quoted for the identical purpose. Applicants describe no "derivatives thereof" other than mentioning in the specification that derivatives may include "salts of the compounds according to the invention and also so-called prodrug compounds." While a method of making the instantly elected species is disclosed, there is no disclosure of a method for making any derivative. No derivatives are described adequately enough to allow one skilled in the art to ascertain that Applicant is in possession of the entire scope of the claimed genus. Applicants have not described this genus in a manner that would allow one skilled in the art to immediately envisage the compounds contemplated for use. As such, the claims lack adequate written description for the myriad of compounds embraced by the claimed "derivatives thereof."

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and

does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

9. Claims 1-5, 7-11 and 30-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5, 7-11 and 30-38 recite the limitation, "mixtures thereof in **all** ratios" in reference to the instantly claimed compounds. Applicant has not described the claimed genus of "all ratios" in a manner that would indicate they were in possession of the full scope of this genus.

In the instant case, the claims are drawn to the compound (5-Chloro-7-nitrobenzoxazol-2-yl)-[4-(pyridine-4-ylsulfanyl)phenyl]amine or a composition of said compound, which falls within the general structure of formula (I), or a pharmaceutically acceptable salt, derivative, solvate, or stereoisomer thereof, as well as mixtures thereof in all ratios. The claimed "mixtures thereof" encompass any mixture containing the claimed compounds, or pharmaceutically acceptable salts, derivatives, solvates, or stereoisomers thereof. Applicants describe no "mixtures thereof" other than mentioning in the specification that the claimed mixtures would include "mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000." No further mixtures are described adequately enough to allow one skilled in

the art to ascertain that Applicant is in possession of the entire scope of the claimed genus. Applicants have not described this genus in a manner that would allow one skilled in the art to immediately envisage every specific mixture of the compounds contemplated for use. As such, the claims lack adequate written description for the myriad of mixtures embraced by the claimed "mixtures thereof."

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

10. Claims 1-5, 7-11 and 30-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutically acceptable salts, does not reasonably provide enablement for pharmaceutically acceptable solvates and derivatives. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

11. As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. The nature of the invention
2. The state of the prior art
3. The predictability or lack thereof in the art
4. The amount of direction or guidance present
5. The presence or absence of working examples
6. The breadth of the claims
7. The quantity of experimentation needed, and
8. The level of skill in the art

*The Nature of the Invention*

The nature of the invention is the compound of formula (I) in Claim 1, namely the instantly elected compound (5-Chloro-7-nitrobenzoxazol-2-yl)-[4-(pyridine-4-ylsulfanyl)phenyl]amine and a pharmaceutically acceptable salt, derivative, stereoisomer, or solvate thereof. Said compound or mixtures thereof can be formulated into a pharmaceutical composition (Claims 9-10) or a kit (Claim 11).

*The State of the Prior Art and the Predictability or lack thereof in the art*

Active pharmaceutical ingredients are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact, and generally stable format to store an active pharmaceutical ingredient or a drug product. Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. Active pharmaceutical ingredients can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and

amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability, and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as polymorphs and solvates are not so common to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate super-saturation and promote crystallization (Morissette et al. *Advanced Drug Delivery Reviews* 2004, 56, 275-300). Therefore, for these reasons, the state of the prior art is one of unpredictability.

As stated above, crystalline solids can exist in the form of polymorph, solvates or hydrates. "Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate, and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. Hence, it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development" (Vippagunta et al. *Advanced Drug Delivery Reviews* 2001, 48, 3-26, abstract). In further discussing the predictability of the formation of solvates,

Vippagunta et al. discloses that "predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds" (page 18, section 3.4).

*The Amount of Direction or Guidance Present and Presence or Absence of Working Examples*

The only direction or guidance present in the instant specification is for compounds of claim 1, as well as pharmaceutically acceptable salts and pharmaceutical compositions. There is no data present in the specification for the preparation of solvates of compounds of claim 1. The specification only discloses that "Solvates of the compounds of the formula (I) is taken to mean adductions of inert solvent molecules onto the compounds of formula (I) which form owing to their mutual attractive force," and lists hydrates and alcoholates as examples (page 23, lines 20-24). The guidance in the specification is limited to the disclosure that generic compounds of formula (I) can exist in solvated form; however, it is not discussed which specific compounds can exist in this form. Additionally, preferred embodiments and examples do not support enablement for solvates of *certain* compounds. Finally, there are no working examples present in the disclosure for the preparation of solvates. In each of the working examples, the compound is placed in solution, but finally the solvent was removed to give a solid (and in the case of the instantly elected compound, an amorphous solid), resulting in the original compound, not a solvated form.

*The Breadth of the Claims*

The instant breadth of the rejected claims is broader than the disclosure, specifically; the

instant claims include any solvates of the claimed compounds.

*The Quantity of Experimentation Needed and the Level of Skill in the Art*

While the level of skill in the pharmaceutical arts is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prepare *any* solvate of the compounds of claim 1. The science of crystallization has evolved such that, without guidance or working examples in the specification, the claims lack enablement. This rejection can be overcome by deletion of the word "solvate" from claims 1 and 7.

***Claim Rejections – 35 USC § 112***

***(second paragraph)***

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7-11, and 30-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is drawn to the instantly elected compound; however, the claim is also drawn to "mixtures thereof in all ratios." Thus, it is unclear whether Applicant is intending the claim the compound (5-Chloro-7-nitrobenzoxazol-2-yl)-[4-(pyridine-4-ylsulfanyl)phenyl]amine or a composition of said compound. For purposes of prosecution on the merits, the Examiner will interpret the claim as being drawn to the elected species rather than a composition.

***Claim Rejections – 35 USC § 102***

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 1-7 and 30-38 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Reckhow, "Miscellaneous Instrumental Methods," University of Massachusetts Amherst College of Engineering, CEE-572, 5 May 2001.

15. Please note that because no explicit definition of "derivatives" was given in the instant specification, a definition which is consistent with the art has been applied in this rejection. Mirriam-Webster online dictionary defines "derivative" as being "a substance that can be made from another substance" (http://www.merriam-webster.com/dictionary/derivative[1], Definition 4b). In the section entitled "(a) Basic Principles," Reckhow explains that "with complete oxidation all carbon is converted to carbon dioxide" when a sample of an organic compound is exposed to an oxidizing environment at very high temperatures. The process that Reckhow describes would be synonymous with burning an organic compound, such as that of the instant claims which would ultimately produce $CO_2$. Thus, based on the teachings of Reckhow and the definition of "derivative" applied above, it is determined that carbon dioxide is a derivative of the claimed compounds, and thus meets the limitations of the rejected claims, which are drawn to compounds of formula (I) and derivatives thereof.

***Double Patenting***

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7, 9-10, and 30-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5-6, 8-9, and 11 of copending U.S. Application No. 12/328,320. Please note that this is a **provisional** double patenting rejection, as the copending claims have not in fact been patented. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly elected compound [(5-Chloro-7-nitrobenzoxazol-2-yl)-[4-(pyridine-4-ylsulfanyl)phenyl]amine], is a *prima facie* obvious variant of compounds of claims 1-3, 5-6, and 8-9 of the '320 application and in particular, of the preferred embodiment of (6-nitro-1H-benzimidazol-2-yl)[4-(pyridine-4-yloxy)phenyl]amine (Example 33, page 43, lines 10-15 in the specification of '320). The difference between Example 33 in '320 and the instantly elected compound is that the positions and presence of the substituents on the benzimidazol rings vary. Additionally, the O in the benzoxazole ring is substituted for an NH group and the sulfanyl linkage is substitited for and oxy linkage. The two compounds are positional isomers and bioisosteres of one another.

With respect to positional isomers, MPEP 2144.09.II states, "Compounds which are position isomers (compounds having the same radicals in physically different positions on the

same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195USPQ 426 (CCPA 1977).

In positional isomerism, a functional group changes position on the chain or ring. In the instant case, the nitro group changes from the 7 to the 6 position on the benzoxazole ring. The positional isomers of the instant claims and of the '320 application are useful as tyrosine kinse and/or Raf kinase inhibitors. As stated in *In re Norris* 179 F.2d 970, 84 U.S.P.Q. 458 (C.C.P.A. 1970), a novel useful compound that is isomeric with the prior art compound is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compound. In other words, if the positional isomers of the instant application produced unexpected results that would not be obvious to one of ordinary skill in the art, they would be patentably distinct; however, there is no evidence of such results in the instant application.

Additionally, the remainder of the differences between the instantly claimed compound and Example 33 in '320 can be attributed to bioisosteric substitutions, which are well known in the art. Patani et al. teaches that bioisosteres elicit similar biological activited which can be attributed to common physicochemical properties, and that "the critical component for bioisosterism is that bioisosteres affect the same pharmacological target as agonists or antagonists and, thereby, have biological properties which are related to each other (p. 3148, first full paragraph and second to last paragraph). In the instant case, O and NH are isosteric in the benzoxazole ring (See Table 2, page 3148); Cl and H are isosteric as a substituent on the benzoxazole ring (See Table 12, page 3153); and S and O are isosteric in the linkage between the

phenyl and pyridyl rings (See Table 19, page 3156). See Patani et al., *Chem Rev.*, 1996, 96, 3147-76, especially pages 3148, 3153, and 3156.

The motivation to make the instantly claimed compounds derives from the expectation that structurally similar, isosteric compounds would possess similar activity (i.e. they would be pharmacologically active tyrosine and/or Raf kinase inhibitors). Because all of the Example 33 of '320 conforms to formula (I) in said application, one skilled in the art would be motivated to make pharmaceutical compositions of each of those specific compounds, as taught by claim 11 of the '320 application.

Claims 1-5, 7, 9-11, and 30-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5-8, and 10-12 of U.S. Patent No. 7,470,702. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly elected compound [(5-Chloro-7-nitrobenzoxazol-2-yl)-[4-(pyridine-4-ylsulfanyl)phenyl]amine], is a *prima facie* obvious variant of compounds of claims 1-3, 5-8, and 10-12 of the '702 patent and in particular, of the preferred embodiment of (6-nitro-

1H-benzimidazol-2-yl)[4-(pyridine-4-yloxy)phenyl]amine (Example 33, column 26-27, lines 55-65 and 1-2 in the specification of '702). The difference between Example 33 in '702 and the instantly elected compound is that the positions and presence of the substituents on the benzimidazol rings vary. Additionally, the O in the benzoxazole ring is substituted for an NH group and the sulfanyl linkage is substitited for and oxy linkage. The two compounds are positional isomers and bioisosteres of one another.

With respect to positional isomers, MPEP 2144.09.II states, "Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195USPQ 426 (CCPA 1977).

In positional isomerism, a functional group changes position on the chain or ring. In the instant case, the nitro group changes from the 7 to the 6 position on the benzoxazole ring. The positional isomers of the instant claims and of the '702 patent are useful as tyrosine kinse and/or Raf kinase inhibitors. As stated in *In re Norris* 179 F.2d 970, 84 U.S.P.Q. 458 (C.C.P.A. 1970), a novel useful compound that is isomeric with the prior art compound is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compound. In other words, if the positional isomers of the instant application produced unexpected results that would not be obvious to one of ordinary skill in the art, they would be patentably distinct; however, there is no evidence of such results in the instant application.

Additionally, the remainder of the differences between the instantly claimed compound

and Example 33 in '702 can be attributed to bioisosteric substitutions, which are well known in the art. Patani et al. teaches that bioisosteres elicit similar biological activited which can be attributed to common physicochemical properties, and that "the critical component for bioisosterism is that bioisosteres affect the same pharmacological target as agonists or antagonists and, thereby, have biological properties which are related to each other (p. 3148, first full paragraph and second to last paragraph). In the instant case, O and NH are isosteric in the benzoxazole ring (See Table 2, page 3148); Cl and H are isosteric as a substituent on the benzoxazole ring (See Table 12, page 3153); and S and O are isosteric in the linkage between the phenyl and pyridyl rings (See Table 19, page 3156). See Patani et al., *Chem Rev.*, 1996, 96, 3147-76, especially pages 3148, 3153, and 3156.

The motivation to make the instantly claimed compounds derives from the expectation that structurally similar, isosteric compounds would possess similar activity (i.e. they would be pharmacologically active tyrosine and/or Raf kinase inhibitors). Because Example 33 of '702 conforms to formula (I) in said application, one skilled in the art would be motivated to make pharmaceutical compositions and kits of each of those specific compounds, as taught by claims 11 and 12, respectively, of the '702 patent.

***Conclusion***

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALICIA L. FIERRO whose telephone number is (571)270-7683. The examiner can normally be reached on Monday - Thursday 6:00-4:30 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on (571)272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AF

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4121